UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,425	02/07/2002	Muriel Moser	DECLE55.1C2CD1	4226

20995 7590 06/27/2007

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
06/27/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/072,425	MOSER ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/05, 10/30/06, 3/15/07, and 6/04/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-14,16-24,26-35 and 37-57* is/are pending in the application.

4a) Of the above claim(s) *3,8,19,29 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9-14,16-18,20-24,26-28,30-35,37-39 and 41-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 3/15/07 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's IDS's filed 9/09/05, 10/30/06, 3/15/07, and 6/04/07 have been entered.

2. Claims 3, 8, 19, 29, and 40 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39, and 41-57 read on the elected invention and are being acted upon.

3. The previous rejections under 35 U.S.C. 103(a) have been withdrawn. As appropriate arguments relevant to the new rejections that have not been addressed previously will be addressed here.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 13, 14, 23, 24, 34, and 35 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, specifically, the "said drug" in Claims 13, 23, and 34 has no antecedent basis in Claim 10, 21, and 31, respectively.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. Applicant argues that explicit antecedent basis is not always necessary.

In this instance, "drug-sensitive" is used as an adjective, "drug" is a noun. There is no antecedent basis for the noun, i.e., the "drug" of the claim.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39, and 41-57 stand rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a rejection for inadequate written description due to the introduction of new matter into the claims.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:

A) The method of producing a fused cell product "for the reduction of the number of tumor cells in a patient", in Claims 1, 10, and 21.

B) The method of producing a fused cell product "using PEG", in Claims 9, 20, 30, and 41.

C) The method of producing a fused cell product comprising:
"(b) analyzing tumor-associated antigens of said tumor sample,
(c) providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample", in Claim 31.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. Applicant reiterates the arguments of 6/13/05. See the response in the Office action of 9/08/05.

8. Claims 21-24, 26-31, 44, and 52 stand rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:

A method for producing DC/tumor hybrids comprising …
(c) providing an immortal cell line/autologous HLA-compatible or allogeneic

DCs comprising immortal autologous or HLA compatible or allogeneic DCs by isolation of DCs from bone marrows lymph or blood or preparing said DCs by differentiating in vitro proliferating DC precursors isolated from bone marrow, lymph or blood.

Applicant indicates that support for the new limitation can be found at pages 25, 28-30 or 60 of the specification.

A review of the specification reveals no support for the immortal cell line DCs of the claim being isolated from these sources.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. Applicant now additionally cites pages 26 and 28 of the specification.

The cite at page 26 discloses the isolation of DCs for culture, not for immediate use in the fusion of step (d). The cite at page 28 discloses the use of cultured DCs, not the directly isolated DCs of step (c) of the claims.

9. The following are new grounds for rejection.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990).

Guo et al. teaches a method for producing a plurality of hybrids/hybridomas comprising a bone marrow derived antigen-presenting B cell and a tumor cell (see particularly page 520, columns 2-3, 11.). The method comprises the providing of a tumor sample and an isolated autologous B cell, and the fusing of the cells with PEG to produce a plurality of hybrids/hybridomas (see particularly page 518, column 2). The reference teaches that the hybrids/hybridomas comprise cells that express both tumor-specific antigens and the machinery for antigen presentation, i.e., characteristics of both tumor cells and B cell APCs (see particularly page 518, column 1), that said

hybrids/hybridomas are useful for the induction of an anti-tumor response in that they reduce the number of tumor cells upon administration to a subject (see particularly page 518, column 3). The reference further teaches that the hybrids/hybridomas were selected on the basis of a tumor cell surface marker and a B cell surface marker (see particularly page 518, column 3).

The reference teaching differs from the claimed invention only in that it does not teach the use of a DC as the antigen presenting component of the hybrid nor the isolation of said DCs from blood.

Sornasse et al. teaches that, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo* (see particularly pages 16-17, Results). The reference teaches the superiority of DCs over B cells for *in vivo* use, "Our data emphasize the main role of DC in initiating primary responses *in vivo*" (see page 18, column 1). Note that the DCs of the reference comprise splenic DCs which would include bone marrow derived DCs, lymphoid DCs, and myeloid DCs.

Young et al. teaches the routine isolation of DCs from human PBMC (peripheral blood mononuclear cells) (see page 1316, *PBMC and Preparation of Leukocyte Subpopulations*)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., by the method of Guo et al., substituting a DC for the B cell in said hybrids/hybridomas, as taught by Sornasse et al, said DCs being isolated from human blood, as taught by Young et al. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution because, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo*, as taught by Sornasse et al. "Our data emphasize the main role of DC in initiating primary responses *in vivo*". Note that the additional limitations such as preparing a primary cell culture of the tumor cells comprises only an obvious and necessary step when said culture is not readily available as it was for Guo et al. Note, however, the BERH-2 tumor cells of Guo et al. derive from a hepatocarcinoma thus, said cells were previously the "primary culture" of tumor cells as set forth in the claims. Finally note that Young et al.

teaches the routine use of human blood as a convenient source of DCs.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. New arguments will be addressed here. Arguments made previously have been addressed previously.

Applicant argues against the references individually.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues "obvious to try".

Note that Guo et al. teaches that the B cell hybrids retain the characteristics of the APC fusion partner, e.g., the B cell. Thus, the ordinarily skilled artisan would expect the DC hybrid to retain the APC characteristics of the DC as well.

Applicant cites the first Moser declaration.

Said declaration was addressed in the Office action of 6/04/04.

Applicant argues that the claims recite the isolation of DCs from bone marrow, lymph, or blood and that spleen is a disfavored source of DCs for fusion partners.

Said argument is addressed in the new rejection.

Applicant argues that Peters, 1981 does not teach DC tumor cell hybrids.

Peters 1980 and 1981, both of record, teach the routine fusion of DCs to tumor cells. The resulting hybrids were capable of activating T lymphocytes. As set forth in the 1980 reference, adherent, esterase-positive, nonphagocytic cells were DCs. After the routine fusion of the DCs to tumor cells the resulting hybrids displayed the capacity to induce T cell growth and at least one of the hybrids stained positive with anti-Ia (MHC Class II), i.e., the resulting hybrids displayed both the

activity and the surface identity of mature DCs. Also note that the instant specification does not disclose that the preparation of the hybrids disclosed therein was anything other than routine. Indeed, the method of the instant claims recites simply **fusing dendritic cells with tumor cells**, thus, demonstrating that any routine fusion method could be employed. Clearly, if there were any remarkable aspects about the instant method of producing DC/tumor cell hybrids said aspects would have been disclosed and claimed.

12. Claims 2, 12, 33, 42, 43, 44, 46, 47, 48, are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990), as applied to Claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29 above, and in further view of U.S. Patent No. 5,851,756.

Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the induction of DC characteristics before using said hybrids/hybridomas, nor the induction of said characteristics using GM-CSF.

The '756 patent teaches the induction of DC characteristics using GM-CSF (see particularly Example I). The reference further teaches that DC exist in relatively small numbers in blood, thus the induction of DC (and thus, DC characteristics) in GM-CSF before use provides a method to increase the number of said DCs (see particularly column 4, line 63 - column 5, line 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al., substituting a DC induced with GM-CSF before use, as taught by the '756 patent, for the B cell in said hybrids/hybridomas. One of ordinary skill in the art at the time of the invention would have been motivated to induce DC (and thus, DC characteristics) with GM-CSF before use because DC exist in relatively small numbers in blood, thus the induction of DC in GM-CSF before use provides a method to increase the number of said DCs, as taught by the '756 patent.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. Applicant

argues that the reference teaches the use of GM-CSF for proliferation of DCs not differentiation.

In view of recent U.S. Supreme Court holdings it is the Examiner's burden merely to provide a reason for using GM-CSF in the culture of the claimed method. Additionally, the court held that what would result through "ordinary innovation" is not patentably distinct. In this case it certainly comprises no more than "ordinary innovation", at most, to add the well-known DC-stimulating cytokine GM-CSF to a DC culture.

13. Claims 50-52, and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990), as applied to Claims 1, 4, 5, 6, 7, 9, 10, 11, 15, 16, 17, 18, 20, 21, 22, 25, 26, 27, 28, and 29 above, and in further view of U.S. Patent No. 5,637,483.

Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the treatment of the hybrids/hybridomas with irradiation before using to prevent proliferation.

The '483 patent teaches the treatment of a tumor cell-containing anti-tumor vaccine with irradiation before using to prevent proliferation (see particularly column 3, lines 65-67 and column 14, lines 3-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al. and employ irradiation before using, as taught by the '483 patent. One of ordinary skill in the art at the time of the invention would have been motivated to treat the hybrids/hybridomas with irradiation before using to prevent proliferation, as taught by the '483 patent.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. Applicant argues that as the rejections under Guo et al. and Sornasse et al. are deficient, this rejection is deficient.

See the Examiner's response above.

14. Claims 13, 14, 23, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al (1990), as applied to Claims 1, 5, 6, 7, 9, 10, 11, 16, 17, 18, 20, 21, 22, 26, 27, 28, and 29 above, and in further view of Reid et al.

Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the use of HAT for the killing of unfused drug-sensitive immortal tumor cells.

Reid et al. teaches the use of the HPRT gene to create a drug-sensitive cell for convenience of selection and killing employing multiple selectively toxic agents including HAT (see particularly page 4299, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al. employing the HPRT gene of Reid et al. One of ordinary skill in the art at the time of the invention would have been motivated to employ the HPRT gene in the hybrids/hybridomas given the teachings of Reid et al. that the introduction of the HPRT gene creates a drug-sensitive cell for convenience of selection and killing employing multiple selectively toxic agents including HAT.

Applicant's arguments, filed in the Brief of 3/15/07, have been fully considered but they are not persuasive. Applicant argues that as the rejections under Guo et al. and Sornasse et al. are deficient, this rejection is deficient.

See the Examiner's response above.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 7, 9, 10, 13 ,14, 18, and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Breel et al. (1988, IDS).

Breel et al. teaches a method of producing a plurality of DC/tumor cell hybrids comprising providing a sample of tumor (SP2/0 myeloma cells, necessarily obtained from cell culture), providing isolated autologous (all cells are autologous to their source) lymph node DCs, and fusing the DCs with the tumor cells by a standard hybridoma fusion protocol (which would include PEG fusion and HAT selection) to produce a plurality of hybrids (see particularly Materials and Methods, page 168). The reference further teaches the selecting of a hybrid which exhibits a DC cell surface marker (NLDC-145) (see particularly Results, page 170). Note that the recitation of "providing a sample of a tumor *against which a response is needed*" is not considered to comprise an actual method step. The recitation of producing ... cell hybrids *which induce an anti-tumor response when provided to a patient causing a reduction of the number of tumor cells in said patient*" is considered to be an inherent property of the hybrids.

The reference clearly anticipates the claimed invention.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Please Note: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
6/22/07